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Formulation and Compaction of Nonfracturing Deformable Coated Beads

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ABSTRACT

There has been considerable interest in making tablets from spheronized beads rather than through encapsulation. It is obvious that the forces present during compaction may break a coating intended to control drug release. This effect may be moderated by cushioning agents incorporated into the bead formulation or situation between the beads. Our work describes the latter method.

INTRODUCTION

Because a considerable body of information has been published about spheronization over the last 20 years, a brief review of the related work undertaken in these and other laboratories pertinent to the current study is in order.

In Fig. 1, the process of spheronization and related topics are diagrammed schematically, identifying logically the processes of interest to this study.

Malinowski and Smith used complete factorial design (1,2) in order to study the qualities imparted to the bead product by modification of a specific granulation. By measuring the effects of extruder screen temperature, extruder escape, bead flow rate, bulk density of the beads, mean particle size, particle size profile, and granule friability, they were able to identify water content and spheronizer speed as the main contributors to optimization of those bead product properties.

O'Connor et al. (3) found that some microcrystalline cellulose grades are more suitable than others for spheronization, with some not being suitable at all. Variation of residency time was needed in some cases to produce spheres of comparable visual quality depending upon the binders and diluents used to make the beads. Even then, some "beads" were rodlike in shape. Beads were tested using sieve and particle-size analysis, friability, density, and dissolution; variations in behavior were dependent upon the grade of microcrystalline cellulose used.

Woodruff and Nuessle (4) studied the effects of the plate rotational speed and dwell time on the resulting granules while comparing the spheronized material to that of conventional granules. They used a double-ex-

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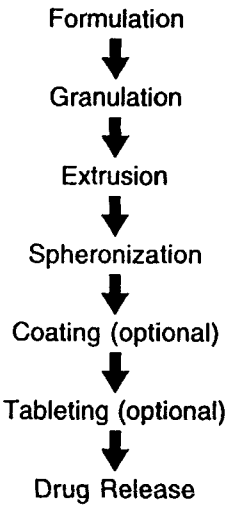

Figure 1. Spheronization processes and related topics.

truded granulation consisting of sucrose, lactose, and microcrystalline cellulose wetted with a mineral oil–water mixture. Comparisons were made of the spheronized products with one another and with the hand granulation, noting differences in flow, granulation and bulk densities, and particle size and shape. The most notable effect was that the product shape was sensitive to plate speed, with higher speeds creating the most spherical shape. The spheronized granulations had slightly higher granule densities than the hand-formed granulation (it was assumed that this may have been due to extrusion), and the spheronized material exhibited better flow. Bulk densities were much greater for the spheronized products and increased with increasing plate speed. As product shape became more spherical with increasing plate speeds, packing void porosity decreased, and while hand granulation was least regular/spherical, it had the highest porosity.

The work of Bataille et al. (5) investigated the influence of the speed and duration of residency in the spheronizer on the quality of the microcrystalline cellulose granules. The spheres produced were uniform and the batch yield was high. The size profile, bead hardness, friability, flowability, and tap density were evaluated with respect to the two variables. Only flowability showed no significant effect over the range of residence time and spheronizer speed investigated.

The critical nature of the moisture level in the granulation used for spheronization is evidenced in the studies by Malinowski (1,2,6,7) and O'Connor (3,8–10). The granulation liquid imparts some of the plasticity mentioned above (3,11–13). Malinowski and Smith (2) identified the initial water content of the granulation (and spheronizer rotational speed) as having a major effect on many of the significant qualities of the final product, including the dissolution rate of tablets made from such beads (1). O'Connor's series of experiments (3,8–10) confirmed these results with extended dissolution rate studies. The final moisture content of an agglomerated material is important in the tableting process as well, since it affects the compaction behavior of the granules (14).

The composition of the granulation liquid also will have an effect on the strength of the dried spheres and whether spheronization will be successful at all (15). Beads made with 95:5 ethanol:water as the granulating fluid were more friable, smaller, and less regular in shape, and had a porosity nearly 4 times that of a 100% water formulation (porosity: 54% vs. 14%) (15). There was an inverse linear relationship between bead friability (9) and the mole fraction of water in the ethanol/water granulating fluid in Millili, and Schwartz's study (15). This supports the work of Conway-Jones (16) and Schubert (17) which showed that *moist* granule tensile strength correlated with granulating fluid surface tension.

Some of the plasticity necessary to produce a uniform sphere is provided by the powdered excipients as well as the granulation fluid. Numerous studies (18–21) have stated that the materials used for marumerization must possess *inherent* cohesive and plastic properties to form the extrudate mass. O'Connor et al. (3) and Zhang et al. (22) looked at excipients for spheronization. O'Connor et al. (3,9) used single components for producing spheres to examine the acceptability of certain commercial materials for spheronization. AVICEL® PH, RC-, and CL-types all were extrudable and spheronizible by varying the amount of water in the formulation, but not all AVICEL materials processed into equivalent products. O'Connor's evaluation of the spheres concluded that the quality of those produced by the PH-types (4 types) far exceeded that of the RC-types (3 types) and CL-type (1 type), even if the moisture level was optimal. Beads made with grades of microcrystalline cellulose containing sodium carboxymethylcellulose (AVICEL RC-581, RC-591, CL-611) with low drug content produced rodlike products, but with higher drug levels, the product was more spherical. The tapped density of beads made from AVICEL PH-101 was

greater than that for conventional granulations reported in the literature (3).

Additionally, it was found in O'Connor's study that dibasic calcium phosphate dihydrate, lactose monohydrate, starch, and pregelatinized starch were unsuitable as single components for sphere production at the water levels used, although it was felt that moisture level optimization may have resulted in the production of a satisfactory bead product. Further study by Nguyen (23) has shown that the first two excipients listed above are amenable to spheronization when used in combination with various grades of microcrystalline cellulose, imparting different consolidation, compression, and compaction properties to the tableted product.

Zhang et al. (22,24) made spheres by the pan-rolling method as well as by marumerizing, with pan-rolled product being less dense than the machine-made beads from the same formulation. They also disintegrated rather than behaving as inert porous matrices.

Additionally, Zhang et al. (22,25) determined that although the corn starch–sucrose blends form spheres by the traditional pan method, the elasticities were too low for the formulations to be extruded and spheronized (21). It was found that some of the granulations broke into short segments when extruded but were not plastic enough to yield a spherical product (18–21).

Many of the studies performed have used microcrystalline cellulose in combination with drugs of differing solubilities in various proportions. A placebo formulation consisting only of microcrystalline cellulose was not successfully spheronized when 95% ethanol was used, but when a low concentration (about 10%) of active was added to the microcrystalline cellulose, processing with successful with that granulating fluid (15). Malinowski and Smith studied mixtures of acetaminophen:microcrystalline cellulose at a fixed 80:20 ratio (1), while O'Connor and Schwartz (8) varied the drug:diluent ratio from 10:90 to 80:20 for the drugs theophylline and quinidine sulfate. However, Nguyen (23) reported that granulations containing more than 80% of a *brittle* material did not spheronize satisfactorily.

Ghali et al. (26) made microcrystalline cellulose spheres incorporating waxy materials having a range of melting points (stearic acid, beeswax, polyethylene glycol, cetyl alcohol, spermaceti, glyceryl palmitostearate, etc.) and found that all but PEG 8000 (at 30%) yielded satisfactory spheres.

O'Connor et al. studied the release of drug from uncoated marumerized spheres [3,8–10] as did Zhang et al. (22,24), Ghali et al. (26,27), and Nguyen (23). The use of microcrystalline cellulose as a controlled-release matrix material was first reported by O'Connor et al. (3,8–10) and the beads were found to exhibit inert porous matrix-type release (28), remaining intact in the dissolution fluid for at least 12 hr (8). Uncoated microcrystalline cellulose beads containing 10% theophylline exhibited 100% dose release in about 3 hr in deionized water (8). O'Connor et al. found that release from uncoated beads was dependent upon the amount of drug present (3), the excipient(s) used, and the processing parameters employed (8).

Upon investigating the influence of amount of water used in the granulating step on the release of theophylline from spheres, Herman et al. (29) found an inverse relationship between the release rate and the proportion of water, increasing in significance with increasing proportions of theophylline anhydrous versus microcrystalline cellulose in the binary formulations. The x-ray diffraction patterns of wet-granulated binary formulations showed a similarity to those for pure theophylline monohydrate, indicating that the drug had become hydrated. This hydration was not duplicated when theophylline anhydrous was wet granulated by itself, nor when the anhydrous drug was directly compressed after dry-blending with microcrystalline cellulose.

When uncoated spheres were made with granulating liquid consisting of ethanol/water mixtures with water content less than 30%, the spheres disintegrated almost immediately upon dissolution, releasing almost all of the active ingredient (acetaminophen or theophylline) within 15 min (15).

Zhang et al. reported that while uncoated *marumerized* spheres behaved like an inert matrix (22), pan-rolled spheres made from the same formulation were less dense, tended to disintegrate, and so had a higher release rate than if marumerized (24).

When beads were manufactured using microcrystalline cellulose and various actives at 10% w/w, the dissolution rate from beads was related to drug solubility (8,9), but the beads remained intact over 12 hr in the dissolution fluid. The pores left by dissolved drug particles were obvious using scanning electron microscopy (SEM). These bead formulations exhibited inert matrix release for low- to medium-drug levels (10).

Low-drug-content beads made with grades of microcrystalline cellulose containing sodium carboxymethylcellulose (AVICEL RC-581, RC-591, CL-611) produced rodlike products, while at higher drug levels, the product was more spherical. Upon dissolution in water, these beads formed a gel (28,30,31); however, no gel

was formed when dissolution was performed in acid or buffer. The hydrogel release has been determined to be a function of the ionic strength of the dissolution medium (32). When a 0.16 M ionic strength dissolution medium was used, the pellets became swollen and remained as distinct units, unlike in water, where they merged to form a mass which completely filled the basket.

Schwartz (33) reported controlled-release characteristics when beads are manufactured with waxy materials. When waxes of various types were incorporated into bead formulations, it was done with the intention of forming a matrix in the bead or in a tablet upon compaction. The waxy beads (up to 30% w/w) manufactured by Ghali et al. (26) retained the same release profile as beads without wax before heat treatment; but when waxy beads were heated to 80°C, those made with spermaceti (melting range, m.r.: 42°–52°C), glyceryl palmitostearate (m.r.: 52°–55°C), beeswax (m.r.: 62°–65°C), or castor wax (m.r.: 86°–88°C) exhibited a slowing of release. No reduction in dissolution rate was seen after the same thermal treatment of bead formulations made with stearic acid (m.r.: 69°–70°C), glyceryl monostearate (m.r.: 56°–58°C), cetyl alcohol (m.r.: 45°–50°C), or polyethylene glycol 8000 (m.r.: not applicable). The release of active at a faster rate supported previously reported results (8,26) that additional ingredients interrupt matrix creation by microcrystalline cellulose bond formation.

Ghali et al. (27) reported a modification of release by combining two grades of microcrystalline cellulose, one of which contained sodium carboxy-methylcellulose (AVICEL RC-581). The results of dissolution varied with the type and proportions of microcrystalline cellulose and the dissolution medium. Since the RC-type materials formed gels in water as described by O'Connor and Schwartz (8), the drug release rate decreased as the proportion of RC-type in the pellet formulations increased, diffusion in gel being slower than with pore release systems. When the dissolution medium used was acidic, little or no gel formation was seen so the release rates were faster and varied only slightly for both high- and low-solubility model drugs. All formulations remained as intact pellets through the 2-hr dissolution test. It was noted that the ionic strength of the dissolution medium, rather than the pH, affected the nonacidic release from pellets made from RC-581 alone (32).

It is known from experimental experience in these laboratories that the forces used in tablet compaction will fracture beads composed mainly of microcrystalline cellulose (34). The rationale for this was proposed by Nguyen (23) as a reduction in mechanical bonding between the microcrystalline cellulose particles. It would be logical to assume that if these beads were coated, then the coating also would be disrupted because of the lack of plasticity of the applied coating. If the purpose of the coating were to regulate dissolution or protect the bead from premature exposure to the environment, any such disruption would defeat the design.

The purpose of this study was to produce satisfactory tablets from coated beads while maintaining the same release profile as that of a sample of uncompacted beads. We hypothesized that coated beads would be protected from fracture during compaction by the inclusion of matrix cushioning agents, thereby maintaining the release profile of unfractured coated beads.

An enteric coating on the drug beads served as a screening device to rapidly determine the condition of the beads before and after the compaction. Should the coating be broken by the force of compaction, the drug would be released into, and detected in, the dissolution fluid. The character of dissolution release of drug from unfractured coated drug beads would be the same as that for uncompacted beads.

EXPERIMENTAL

Materials

The matrix materials included: microcrystalline cellulose (MCC, AVICEL PH-101, FMC Corporation, Philadelphia, PA) and glyceryl palmitostearate (GPS, PRECIROL ATO-5, Gattefossé, SA, Saint Priest, France). The coating material used was methyl methacrylate copolymer (Co-MMA, EUDRAGIT L30D methyl methacrylate copolymer aqueous dispersion, Röhm Pharma, Weiterstadt, Germany).

The model drug used in this study was theophylline anhydrous, USP (Knoll Fine Chemicals, New York, NY).

Pellet Manufacturing

Beads containing 10% theophylline were formed by wet granulation in a planetary mixer (KitchenAid® model A200T, Hobart Corporation, Hobart, NY) from MCC, theophylline, and purified water. Wet granulation was followed by extrusion from a twin-screw extruder (Luwa EXDS-60, Luwa Corp., Charlotte, NC) at 50 rpm using 1.5-mm screens. The extrudate was spheronized (Luwa Q-230, Luwa Corp., Charlotte, NC) for 1 min on a 2-mm scored plate and then spread on

trays to be dried overnight in a 40°C forced-air oven. Sieving (US standard sieves) provided a 16/20-mesh cut for further processing and testing.

A portion of the drug-loaded beads of the 16/20-mesh cut were coated with Co-MMA using a bottom-spray fluid bed apparatus (STA-1, Aeromatic AG, Towaco, NJ) with a Wurster insert to about 3% weight gain based on dry solids. These coated beads were dried in the fluid bed apparatus at 60°C and then spread on paper-lined trays for complete drying in a 40°C forced-air oven overnight.

Wax beads are known to deform (27) and so were used as one cushioning agent. The wax beads were wet granulated from a 1:1 mixture of GPS and MCC with purified water. The same protocols were used as with the drug beads to extrude, spheronize, and dry the wax (GPS + MCC) beads.

Tableting

Tableting was done on an INSTRON® 4206 stress-strain analyzer using 13/32 in. diameter, cylindrical, flat-faced, stainless steel tooling, cleaned and prelubricated before each compaction with magnesium stearate suspended in acetone. The cross arm speed was set to 1 mm/min and when the preset maximum force was reached, the cross arm movement was halted and held in position for 3 sec to approximate a static load.

Compaction was performed at 1000-lb increments from 1000 to 8000 lb on all formulations except the control formulations of 100% coated and 100% uncoated bead tablets. The control or noncushioned formulations were made from 100% uncoated drug beads or 100% coated drug beads. Cushioned tablet formulations were made using either of two cushioning agents interspersed with the drug beads: MCC powder or GPS+MCC beads. Each agent was incorporated individually at three levels: 50%, 75%, and 90% with the remaining amount being composed only of drug beads.

Testing

Physical testing of the uncoated and coated beads included sieve analysis, loss on drying (Cenco moisture balance model 26680, CSC Scientific, Chicago, IL), crushing strength (Manesty Monsanto Stokes' tablet tester, Liverpool, England), and bulk and tap densities via the standard graduated cylinder method.

That the coating was complete before compaction was ensured by dissolution testing to see if there was any disruption of the enteric coating when the beads were compacted. The uncompacted beads were tested as both coated and uncoated beads. Dissolution was performed in 0.1 N HCl using USP/NF Method I at 50 rpm, the sample being taken at 1 hr elapsed time. Either 500 mg of beads (16/20 mesh) or single tablets were used as dissolution samples and were analyzed by ultraviolet (UV) spectroscopy at 272 nm using a double-beam spectrophotometer.

Figure 2 shows the standard absorbance curve for theophylline (standard theophylline anhydrous, Sigma Chemical, St. Louis, MO; lot 24C-2020) in 0.1 N HCl at 272 nm at concentrations between 2 and 20 μg/ml.

RESULTS AND DISCUSSION: PHYSICAL PROPERTIES OF MATERIALS AND BEADS

The measured physical properties of the raw materials and beads are presented in Tables 1–9. Other than for sieve analysis, for which "full" batch data are presented, the data presented for the beads are restricted to the 16/20-mesh cut selected for further processing.

Sieve Analysis

The (uncoated) drug-loaded spheres and GPS + MCC (placebo) spheres were submitted to sieve analysis; the results are shown in Table 1. The drug-loaded

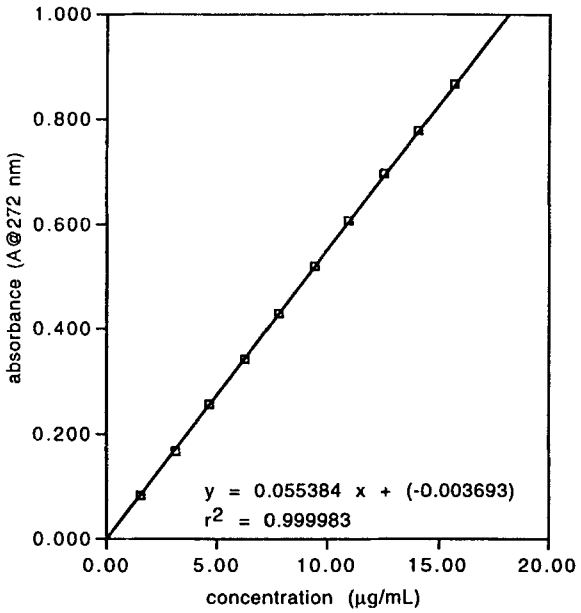

Figure 2. Standard curve for theophylline anhydrous in 0.1 N HCl.

Table 1

Sieve Analysis of Spheres

	On screen	Mesh Cut	Net (g)	% on Screen
Uncoated Drug-Loaded Beads				
Combined	12	>12	3.2	0.2
Sections	14	12–14	35.7	2.0
	16	14–16	379.3	21.3
	20	16–20	1146.9	64.3
	30	20–30	197.2	11.0
	40	30–40	20.0	1.1
	Pan	<40	2.3	0.1
	Total	n/a	1784.7	
GPS + MCC (wax) Beads				
Combined	12	>12	29.5	1.5
Sections	14	12–14	314.9	16.5
	16	14–16	686.2	35.9
	20	16–20	664.8	34.8
	30	20–30	169.0	8.8
	40	30–40	38.1	2.0
	Pan	<40	9.8	0.5
	Total	n/a	1912.3	

spheres provided a "sharp" size profile of nearly symmetrical shape having more than 64% of the batch represented in the 16/20-mesh cut. The 14/16- and 20/30-mesh cuts represented 21% and 11% of the batch yield, respectively. Less than 5% of the spheres in this batch were larger or smaller than these three sections. This is typical of MCC formulations which have been properly moistened for spheronization processing (3,5,15,27). The 16/20-mesh cut was used for coating and tableting.

In contrast, the wax spheres made with 50% (w/w) GPS and MCC tended to have a broader mesh profile which was skewed toward larger diameters. Still, over 70% of the placebo batch yield was in the two cuts with mesh sizes between 14 and 20. While the proportion of the 20/30-mesh cut (8%) remained about the same as for that section of the drug-loaded spheres (11%), the 12/14- and >12-mesh cut proportions of the wax spheres (16.5% and 1.5%) were about 8 times higher than those same fractions from the drug beads (2.0% and 0.2%). This may be indicative of the "stickiness" of the wax component of these placebo beads; the smaller spheres may tend to agglomerate more during marumerization (3), creating a greater proportion of product with larger diameters.

Bulk and Tap Densities

As expected, the bulk densities of the spheronized materials were almost twice that of the raw materials, except in the case of the wax beads which contained GPS. Raw materials were sieved first through a 20-mesh screen. The bead samples used for bulk and tap density measurements were taken from 16/20-mesh cuts. These bulk and tap density data (Table 2) are comparable with spheronized formulations of similar composition while being more dense than conventional granulations (3,15,27,35), which are listed in Table 3.

Moisture Determination

Table 4 summarizes the data obtained for the moisture content of the raw materials and the spheronized products. The various methods of determination utilized were consistent with the components of manufacture of the bead batches. The beads containing GPS could not be tested above the melting point of GPS (52°–55°C), so that a modified test for moisture content had to be devised.

Table 2

Bulk and Tap Densities of Raw Materials and Spheres

Raw Material	Bulk Density (g/ml)	100-Tap Density (g/ml)	Density Increase (%)
Avicel PH-101	0.323	0.431	33.4
Precirol ATO-5	0.312	0.390	25.0
Theophylline, anhyd.	0.489	0.680	39.0
Spheres			
Uncoated drug beads	0.770	0.807	4.8
Coated drug beads	0.795	0.841	5.8
GPS + MCC beads	0.563	0.593	5.3

Table 3

Published Density Values for Spheronized and Traditional Granulations of Similar Formulations

Formulation	Process	Bulk Density (g/ml)	Tap Density (g/ml)	Ref.
100% Avicel PH-101	Spheronization	0.78	0.81	O'Connor et al. (3)
10% theophylline Avicel PH-101	Spheronization	0.75	0.76	Ghali et al. (27)
Avicel PH-101	Spheronization	0.72	0.74	Millili and Schwartz (15)
5% theophylline Avicel PH-101	Traditional wet granulation	0.52	0.56	Unvala et al. (35)

Table 4

Moisture Content of Raw Materials and Spheres

Raw Material	Loss on Drying, %	
MCC: Avicel PH-101	3.51[a]	
Theophylline, anhydrous	0.001[a]	
GPS: Precirol ATO-5	0.022[b]	
	Loss on Drying, %	
Sphere Batch	Cenco Moisture Balance	Forced-Air Oven (@T°C)
Uncoated drug beads	0.8	0.90 (105)[c]
Coated drug beads	1.2	3.20 (105)[c]
GPS + MCC beads	NA[d]	1.0 (45)

[a]105°C oven, USP XXII method.
[b]45°C oven to constant weight.
[c]Cracked beads, 105°C oven, USP XXII method.
[d]NA = not applicable.

The moisture content for the uncoated beads was determined to be 0.8% using the Cenco moisture balance, but the 1.2% value reported for the coated beads by the same instrument should be suspect owing to the very low water permeation rates of poreless methyl methacrylate films (34). Since the Eudragit L30D (Co-MMA) coating was applied to prevent moisture from getting into the bead (36), it is reasonable to expect that the escape of moisture would be precluded as well. Although the 16/20-mesh beads containing drug had been dried at 40°C after manufacture (0.8% residual moisture), the methyl methacrylate copolymer was applied as an aqueous dispersion and it should be expected that some moisture had penetrated the bead matrix and had become trapped as the coating coalesced, closing off routes of escape for water vapor. Thus a modified test (based on the USP XXII method) for loss on drying was performed. The coated drug beads were first cracked in an agate mortar to ensure complete transfer to a tared weighing dish, thereby exposing the "protected" volume, accurately weighing the completely transferred sample, and drying for 4 hr at 105°C. For reference, this same procedure was performed on the uncoated beads. The weight losses were 3.2% and 0.9%, respectively, for the uncoated drug beads. As the results of the two different tests of moisture analysis for the uncoated drug beads are in agreement (0.8% vs. 0.9%), it was concluded that the moisture within the coated beads was not measured accurately by the Cenco balance. As a result of these tests, it was determined that the actual coating applied was 10% by dry weight. Therefore, the value of 10% was used in all calculations involving the coated beads and all assay results.

Crushing Strength of Beads and Tablets

Tables 5 and 6 provide data on the crushing strength of both spheres and tablets. The Monsanto tablet tester was used to crush the tablets as well as 10 beads from each batch manufactured. The drug-loaded spheres fractured at very low loads (2.7 ± 0.4 kg) and at only marginally higher loads when coated (3.3 ± 0.6 kg). The GPS + MCC beads, as expected, were even weaker (0.6 ± 0.2 kg).

The lack of good bonding between the spheres, either coated or wax, was seen in both the crushing strength of the tablets consisting of 100% coated spheres or some fraction of GPS + MCC spheres: the values often did not exceed 5.0 kg except for the 90% wax formulation. Visual evidence for this was observed when examining the fragments of the crushed tablets: concavities from bead impressions and intact beads could be seen in the fractured surfaces. In fact, the most satisfactory hardness values were obtained for tablets consisting entirely of GPS spheres. The sensitivity of the MCC powder to compaction pressure, even in the presence of coated drug spheres was evident from the hardness of those tablets. At pressures above 26.7 MPa (used only for hardness testing due to the sensitivity of MCC), the tablets made from all formulations contain-

Table 5

Crushing Strength Data for Spheres (Stokes-Monsanto, kg)

Uncoated Drug Beads	Coated Drug Beads	GPS + MCC Beads
2.0	3.4	0.4
2.2	4.2	0.9
2.8	3.1	0.4
3.0	4.0	0.7
2.5	2.7	0.5
3.0	3.4	0.6
3.1	3.7	0.6
2.6	2.7	0.8
3.4	3.6	0.4
2.5	2.3	0.4
Mean 2.71	3.31	0.57
SD 0.43	0.61	0.18

Table 6

Crushing Strength Data for Tablets (Stokes–Monsanto, kg)

Comp. Press. (MPa)	100% Coated Drug Beads	50% GPS + MCC Beads	75% GPS + MCC Beads	90% GPS + MCC Beads	100% GPS + MCC Beads	50% MCC Powder	75% MCC Powder	90% 75% Powder
26.70								7.35
53.41	0.00				6.00			13.00
106.82			4.50		5.50		13.00	
160.23					6.30		13.00	
213.64	2.80		4.10					
267.05		2.67		6.07	6.60		13.00	
320.46	1.50		5.20					
373.87								
427.28		3.40	4.83	5.43		13.00		
480.69	2.40							

ing MCC powder were harder than could be tested with the apparatus, being higher than 13.0 kg.

From the tablet crushing strength data, plotted in Fig. 3, it is evident that the hardness of the tablets is directly related to the proportion of GPS + MCC spheres present in the tablet formulation.

Dissolution of Noncushioned Tablets

Uncoated beads released about 95% of the drug contained within the matrix, whereas those which were coated released only about 1% when tested in acid dissolution medium (Table 7).

Compaction of the uncoated beads demonstrates that the fracture of the beads permitted slightly more drug to be dissolved, with more than 97% of the drug released for all compaction forces used (Table 7). Many of these tablets were not intact after ejection, fragmenting into distorted particles either upon ejection or upon handling, however gently. Those which remained intact after tableting and physical measurement became swollen during dissolution, *if* they remained intact during that phase of testing.

Tablets compacted from coated drug beads were more cohesive than those from uncoated beads. Tablets which were subjected to dissolution remained intact but became swollen with the absorption of dissolution fluid so that the diameter increased nearly 100% and the thickness by about 60%. Most importantly, it is obvious that the coating was fractured by the forces of compaction as the dissolution results at 1 hr indicated between 60% and 73% drug released (Table 7).

Dissolution of Cushioned Tablets

Tablets which were cushioned with MCC powder delaminated but did not *necessarily* completely disintegrate during dissolution. The cushioning was effective as only 30% of the drug content was released when 50% MCC powder was used to cushion the coated beads (Table 8).

Significantly more protection was afforded by the use of 90% MCC powder: as little as 7% theophylline was released during the 1-hr dissolution test. Figure 4 demonstrates the cushioning effect of MCC powder through the range of compaction forces (54–268 MPa).

Tablets which were made using GPS + MCC beads for cushioning disintegrated immediately (within 60 to 90 sec) into a multiparticulate system. The particles did not disintegrate further during the dissolution test. As summarized in Table 9, when 50% wax beads were used in the tablets, no more than 22% theophylline was released. At a 90% wax bead level, tablets formed at most compaction forces released only 5% to 9% of the drug content. It is possible that the release of drug which did occur despite cushioning was caused by damage to the bead coating as a result of friction against the die wall during the compaction event. Figure 5 shows

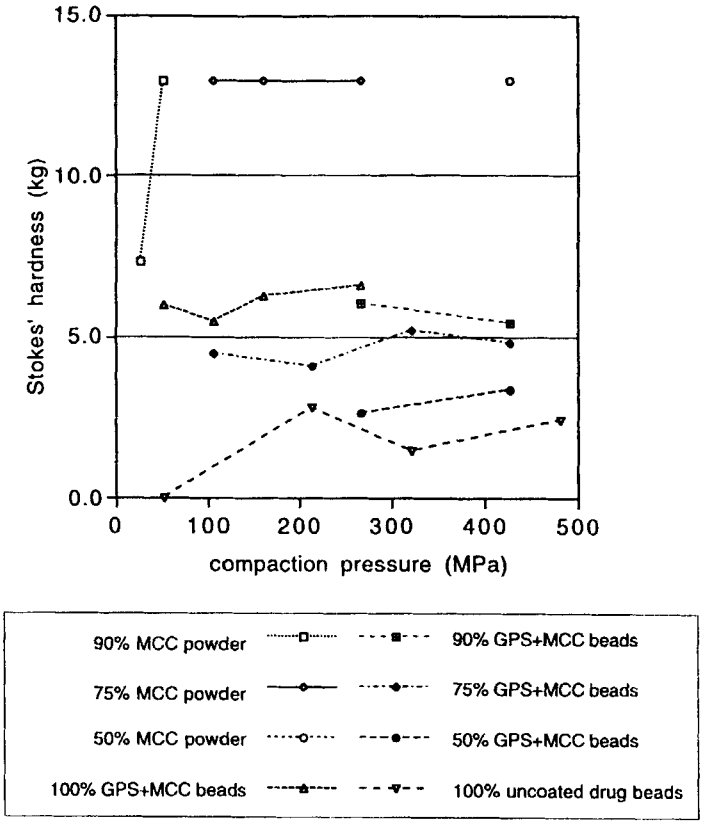

Figure 3. Crushing strength vs. compaction pressure for spheres and tablets.

Table 7

Dissolution of Noncushioned Tablets

Compaction Pressure, P_{max} (MPa)	Uncoated Drug Beads, % Dissolution @ t = 60 min, $n \geq 3$	Coated Drug Beads, % Dissolution @ t = 60 min, $n \geq 3$
0	95.3	1.2
53.5	ND[a]	59.5
107	ND	73.4
161	ND	71.3
187	97.0	ND
214	ND	71.2
250	96.4	ND
268	ND	69.7
312	97.7	ND
375	98.5	ND
437	97.0	ND
499	97.9	ND

[a]ND = no data collected.

Table 8

Dissolution of MCC Powder-Cushioned Tablets

Compaction Pressure, P_{max} (MPa)	50% MCC Powder, % of Dose Dissolved @t = 60 min, $n \geq 3$	75% MCC Powder, % of Dose Dissolved @t = 60 min, $n \geq 3$	90% MCC Powder, % of Dose Dissolved @t = 60 min, $n \geq 3$
53.5	31.5	12.9	8.6
107	32.3	13.1	10.0
161	32.6	16.1	12.2
214	31.8	14.6	14.4
268	28.1	14.9	12.9
321	29.9	11.7	12.0
375	20.9	12.6	7.2
428	17.7	11.3	10.6

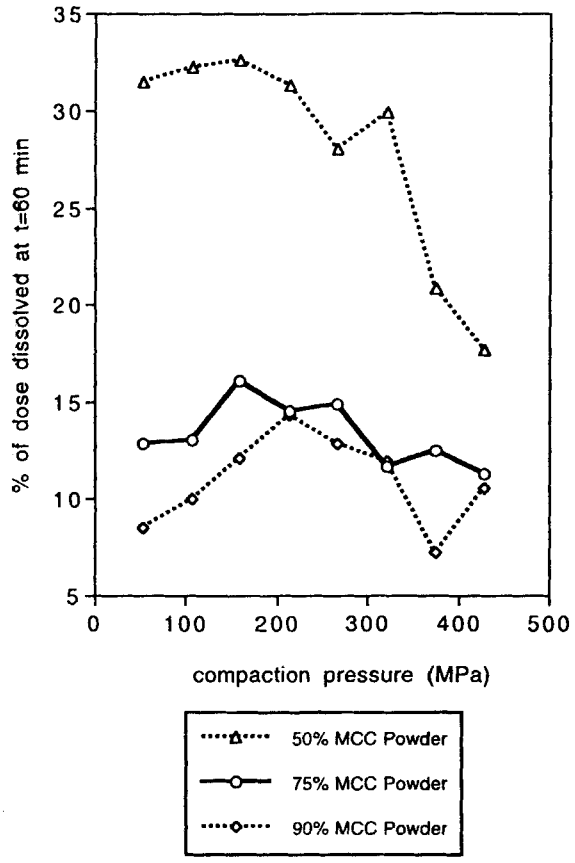

Figure 4. Effect of compaction pressure on dissolution of MCC powder-cushioned tablets.

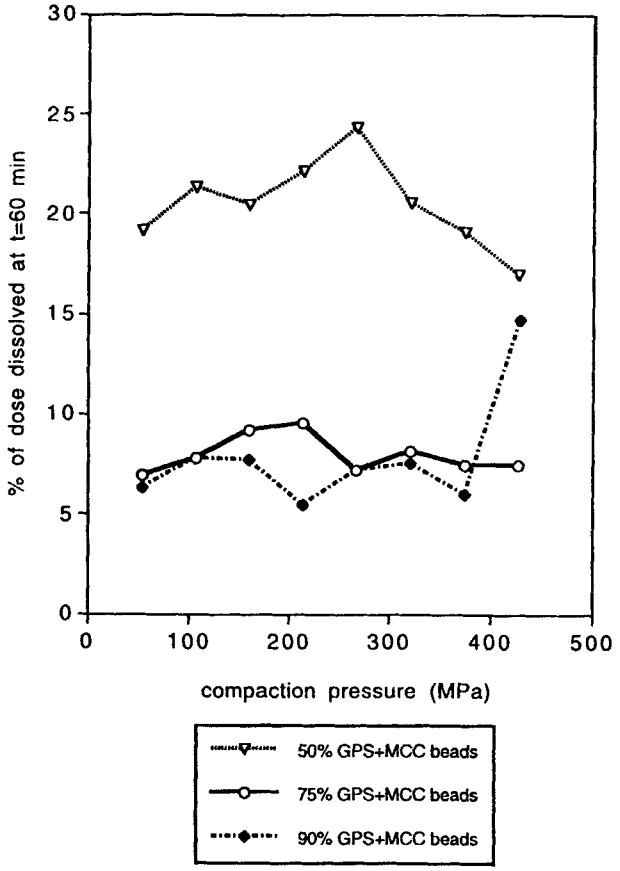

Figure 5. Effect of compaction pressure on dissolution of GPS + MCC sphere-cushioned tablets.

Table 9

Dissolution of GPS + MCC Bead-Cushioned Tablets

Compaction Pressure, P_{max} (MPa)	50% GPS + MCC Beads, % of Dose Dissolved @t = 60 min, $n \geq 3$	75% GPS + MCC Beads, % of Dose Dissolved @t = 60 min, $n \geq 3$	90% GPS + MCC Beads, % of Dose Dissolved @t = 60 min, $n \geq 3$
53.5	19.2	7.0	6.3
107	21.4	7.8	7.8
161	20.5	9.2	7.8
214	22.2	9.6	5.5
268	24.3	7.2	7.2
321	20.5	8.2	7.5
375	19.1	7.5	6.0
428	17.0	7.4	14.7

how dissolution was affected by the inclusion of GPS + MCC beads through the range of compaction forces (54–268 MPa).

It is clear that the inclusion of cushioning agents, such as MCC powder or beads made from GPS and MCC, between brittle MCC spheres is an effective method of formulation modification which permits their compaction without fracture and yet provides satisfactory tablets having the same dissolution profile characteristics as the uncompacted beads.

CONCLUSIONS

Two conclusions may be drawn from the results of this study:

1. Coatings can be protected by cushioning agents like MCC and GPS.
2. Both intact tablets and disintegration to a multiparticulate system can be achieved depending upon the choice of cushioning agent.

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